PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-15457	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/00018	International filing date *(day/month/year)* 13.01.2003	Priority date *(day/month/year)* 24.01.2002
International Patent Classification (IPC) or both national classification and IPC C07D333/20		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.04.2003	20.01.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Gavriliu, D Telephone No. +49 89 2399-8274

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/00018

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-7 as originally filed

Claims, Numbers

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Reference is made to the following documents:**

D1: US-A-5 362 886 (BERGLUND RICHARD A) 8 November 1994 (1994-11-08)
D2: US-A-3 855 227 (HOLLANDER C ET AL) 17 December 1974 (1974-12-17)
D3: US-A-4 036 852 (BOESTEN WILHELMUS H J) 19 July 1977 (1977-07-19)
D4: US-A-5 023 569 (RAVEN GREGORY S) 11 June 1991 (1991-06-11)

2. **Clarity** (Article 6 PCT)

It should be noted that Claim 1 is unclear due to the fact that the steps of the claimed process are not clearly defined. The racemization of a stereomerically enriched mixture (Claim 1-line 8) seems to be related to the recycling of a mixture of salts (from the mother liquid) enriched in the unwanted stereoisomer followed by a second asymmetric induced crystallisation in order to achieve a higher yield in S-enantiomer (as disclosed in description page 4-lines 3-19).

3. **Novelty** (Article 33(1) and (2) EPC).

The subject-matter of the present application is related to a process for producing (S)-3-methylamino-1-(2-thienyl)-1-propanol through the resolution of the corresponding racemic with 2,3,4,5-di-O-isopropylidine-2-keto-L-gulonic acid or (S)-(-)-2-pyrrolidone-5-carboxylic acid.

Since none of the prior art discloses the use of 2,3,4,5-di-O-isopropylidine-2-keto-L-gulonic acid or (S)-(-)-2-pyrrolidone-5-carboxylic acid for the resolution of the racemic of 3-methylamino-1-(2-thienyl)-1-propanol, the novelty of the subject-matter of the present application is acknowledged.

4. **Inventive step** (Article 33(1) and (3)EPC).

The technical problem underlying the present application is to be seen in the

provision of an alternative process for producing optically pure S-enantiomer of 3-methylamino-1-(2-thienyl)-1-propanol.

D1, which is regarded as being the closest prior art, discloses the resolution of the racemic 3-dimethylamino-1-(2-thienyl)-1-propanol (compound which differs from the present enantiomer only through one more N-methyl group), using (S)-(+)-mandelic acid (see column 3 -line 25-column 4-line 3).

D2, discloses the use of (-)-2,3,4,5-di-O-isopropylidine-2-keto-L-gulonic acid, as a resolving agent for organic amines containing one or more centres of chirality (column 1-line 40-column 2-line 14). The solvent used in the diastereoisomers separation is acetone (example 3-column 5-line 55) or acetonitrile (example 4-column 6-line 35) as in the present claims 3 and 5.

D3, discloses the use of 2-pyrrolidone-5-carboxylic acid for the separation of a racemic mixture of L,D-phenyl-glycine amide into enantiomers. Moreover, examples 3 and 7 of D3 disclose the use either of isopropanol or acetone as solvents (as the present claims 3 and 5) for the separation of the racemic through the conversion into diastereoisomers using 2-pyrrolidone-5-carboxylic acid. D3 discloses that the undesired enantiomer may be racemized by heating in an inert acid solvent (column 2-lines 34-46, example 5 of D3).

It would thus have been obvious for the skilled person, faced with the problem of providing an alternative process for the resolution of the racemic of 3-methylamino-1-(2-thienyl)-1-propanol, to combine the use of (-)-2,3,4,5-di-O-isopropylidine-2-keto-L-gulonic acid (D2) or 2-pyrrolidone-5-carboxylic acid(D3) for the separation into enantiomers of a racemate with the teaching of D1, in order to solve the problem.

The problem underlying the present invention for its solution to be considered inventive must therefore be seen in the provision of a further process for producing optically pure enantiomers with unexpected properties compared with the closest prior art.

An inventive step cannot be recognized as it is not yet shown by appropriate information, e.g. in form of experimental data, that the claimed process has un

unexpected effect compared with the closest prior art, which is attributable to the distinguishing feature of the invention.